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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/615,262	07/09/2003	Ryuichi Morishita	Q75926	5695

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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 09/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/615,262	MORISHITA ET AL.	
	Examiner	Art Unit	
	Robert M. Kelly	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 July 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/029,497.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/13/05; 10/9/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 6-7 are presently pending.

Priority

It is noted that in the transmittal letter, Applicant has failed to identify the correct the date of filing of the priority document U.S. Application No. 09/029,497 in the transmittal letter filed. In addition, the preliminary amendment letter also supplied on the date of filing amends the specification to contain a proper reference to the above-listed Application and filing date, but fails to state the Patent number that issued from it, as well as the date of patenting. Lastly, the first paragraph amendment fails to list Application No. 09/660,552 and its status. Hence, the priority information need major correction to comply with the requirements of the USPTO.

Applicant's priority is objected to, but considered as Applicant appears to intend (priority to US Applications 09/660,522 (as divisional parent), 09/029,497 (as continuational parent to 09/660,522), and to PCT/JP96/02359 (as 371 parent to 09/029,497), and also to JP 07-245475 and JP 08-058467 as foreign priority parents to PCT/JP96/02359).

Applicant is required to amend the first page of the specification, or supply an application data sheet containing the proper priority information and dates.

Substitute Specification

Applicant submitted a substitute specification on 7/9/03. Along with the substitute specification, Applicant has filed an informally marked-up copy of the changes in the specification. Further, Applicant states that the amendment to the contains only the amendment that "the word 'myocardia' at page 10, line 7 of the original English application has not been changed." (Applicant's remarks, p. 4).

It appears that Applicant has not made any substantive changes the specification, but the marked changes are extensive in number, and Applicant's remark indicating the only change not made is the word "myocardia" appears to be accurate, as such word is present in the marked up copy, and is not marked, so Applicant did not make a typographical error.

On the other hand, the changes reviewed by the Examiner appear to indicate that the specification conveys the same thoughts, but corrects spelling errors or changes the exact term for a specific disease to another term encompassing the disease (see. E.g., marked up copy of specification, p. 1, paragraph 2).

Hence, Applicant's substitute specification is not entered, pending a formal marked-up copy, and proper explanation of the changes, but is considered for substantive purposes.

Information Disclosure Statements

Applicant's information disclosure statements have been considered, and only the basis of the English translations provided for those citations that are written in foreign languages. In addition, many citations have been crossed-out. These citations were crossed out, even though considered, as indicated by the Examiner's initials in each citation, because either: (i) the citation is improper in its content (e.g., missing author information), or (ii) because such citation is not a publically-available document, and therefore could not be listed on the front page of a patent that may issue.

If Applicant wishes such to placed on the front page of a patent, Applicant should submit proper citations and/or the publically-available document (with English translation, if needed).

Drawings

The drawings are objected to because drawings 12-15 each contain two panels, and the brief description of the drawings does not allow the Artisan to determine which panel indicates what information. Furthermore, Figures 2-3 contain a pound sign (i.e., "#") and it is not clear what marking indicates from the brief description of the drawings.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claim 8 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 7. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim 8 limits the vector of claim 7 to either (i) a viral vector; or (ii) a non-viral vector. The parent claim embraces all vectors, and all vectors are either viral or non-viral, therefore, the claim does not further limit the parent claim, and hence is objected-to.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 7-9 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,248,722. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

Claims 7-9 of the instant Application encompass methods of treating (i) insufficiency of peripheral circulation, or (ii) peripheral angiostenosis in a subject, comprising the intramuscular administration of an expression vector comprising and HGF gene. Further limitations are that the vector is viral or non-viral, and the non-viral vector is encapsulated in a liposome, the membrane of which may be further fused to attenuated Sendai virus particles.

It should be further noted that this Application is a divisional a parent Application, which was a continuation of the Application that issued as U.S. Patent No. 6,248,722.

Claims 1-4 of U.S. Patent No. 6,248,722 are drawn to treating any disease in a subject for which HGF is effective, comprising similar administrations (claims 1-2 and 4). Moreover, such disease may be an arterial disease, of which both diseases in the instant Application are arterial

diseases. Furthermore, the specification of U.S. Patent No. 6,248,722 teaches that such specific diseases may be thus-treated (e.g., col. 4, paragraph 5). Therefore, from U.S. Patent No. 6,248,722, claims 1-4, the Artisan would have found treatment of both (i) insufficiency of peripheral circulation, or (ii) peripheral angiostenosis in a subject, with the same vectors. The Artisan would have been motivated to do so in order to treat these diseases. Furthermore, the Artisan would have had a reasonable expectation of success, as U.S. Patent No. 6,248,722 had taught that such diseases could be thus-treated.

Claims 5-6 of U.S. Patent No. 6,248,722 are drawn to methods of accelerating the growth of vascular endothelial cells in the target tissue of a subject without accelerating the growth of vascular smooth muscle cells, comprising similar administrations as in claims 1-4. Moreover, the specification teaches the use of such methods is to treat, *inter alia*, the diseases listed in the instant Application's claims (e.g., U.S. Patent No. 6,248,722, col. 4, paragraph 5). Therefore, from U.S. Patent No. 6,248,722, Claims 1-4, the Artisan would have found treatment of both (i) insufficiency of peripheral circulation, or (ii) peripheral angiostenosis in a subject, with the same vectors obvious. The Artisan would have been motivated to do so in order to treat these diseases. Furthermore, the Artisan would have had a reasonable expectation of success, as U.S. Patent No. 6,248,722 had taught that such diseases could be thus-treated.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 contains the limitation "the membrane of which may be further fused to attenuated Sendai virus particles". Such limitation, by using the term "may" makes it unclear if such limitation is meant to limit the claim or not. Hence, the claim is rejected for lack of clarity.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating insufficiency of peripheral circulation or peripheral angiostenosis in a subject for which HGF is effective, comprising administering to a peripheral muscle of the subject a plasmid vector comprising an HGF gene comprising a coding sequence for HGF operably linked to a constitutive promoter, wherein the plasmid is encapsulated in an HVJ-liposome, and wherein further cells of the peripheral muscle express the HGF protein, which protein then acts to increase angiogenesis in the muscle to which the vector has been administered does not reasonably provide enablement for any vector, any promoter, any peripheral circulation or angiostenosis, or any treatment non-local to the muscle of administration. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The Law

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is typically a conclusion reached by weighing at least eight factors, as set forth in In re Wands, 858 F.2d at 737, 8 USPQ.2d at 1404.

Such factors are:

(1) The breadth of the claims;

(2) The nature of the invention;

(3) The state of the art;

(4) The level of one of ordinary skill in the art;

(5) The level of predictability in the art;

(6) The amount of direction and guidance provided by Applicant;

(7) The existence of working examples; and

(8) The quantity of experimentation needed to make and/or use the invention.

It is noted that these do not amount a legal 8-prong test, but a weighing of 8 factors, in which any specific factor may outweigh all other factors, and other, non-listed, factors may outweigh all of the listed factors.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention within its

full-claimed scope, and that, therefore, Applicant's claims are not enabled to their fully-claimed scope.

Breadth of the Claims

Applicant's claims embrace treating any insufficiency of peripheral circulation or any peripheral angiostenosis in a subject, comprising administration, to any muscle, any expression vector containing any HGF gene. Such expression vector is further limited to HVJ-liposome-encapsulated vectors.

These claims are broad, encompassing treating any circulation problem in any tissue, by administration to any muscle of the body. They are further broad for the use of any HGF gene, which means any expressible sequence, and necessarily encompasses non-constitutive promoters and promoters with low activity. They are further broad for encompassing any vector.

These broad areas will be shown below to be non-enabled for the full scope claimed at the time of Applicant's constructive reduction to practice.

The Nature of the Invention and State of the Prior Art

The nature of the invention is in gene therapy for treating vascular diseases that result in insufficient blood flow to a tissue.

In gene therapy, is recognized that the vectors utilized are relevant for enabling the claimed invention, because different vectors have different tissue tropisms and efficiencies of transducing any particular cell type. Robbins, et al. (1998) Pharmacol. Ther., 80 : 35-47 teach that the type of vector system has its unique advantages and limitations: "Retrovial vectors can permanently integrate into the genome of the infected cell, but require mitotic cell division for transduction. Adenoviral vectors can efficiently deliver genes to a wide variety of dividing and

nondividing cell types, but immune elimination of infected cells often limits gene expression *in vivo*. Herpes simplex virus can deliver large amounts of exogenous DNA; however, cytotoxicity and maintenance of transgene expression remain as obstacles. AAV also infects many nondividing and dividing cell types, but has limited DNA capacity" (ABSTRACT). Further, Robbins teaches that non-viral vectors, such as naked DNA and liposomes are inefficient in gene transfer to the cell nucleus (p. 36). Miller, et al. (1995) FASEB J., 9 : 190-99, acknowledges various vectors available, but teach "no single delivery system is likely to be universally appropriate." For instance, the requirements of gene therapy for cystic fibrosis are greatly different from those of cancer (p. 190, first paragraph). "Once again, targeting at the level of the vector has not yet been particularly well developed; hence, liposome or viral-mediated delivery of the CFTR gene to airway epitheial cells of CF patients has relied largely on the **localized delivery** of the vectors directly to the affected tissues." (p. 198, first paragraph, emphasis added).

Moreover, Morishita, an inventor, demonstrated in later published art, that the HVJ-liposome encapsulating a plasmid for delivery of the HGF gene is used, rather than naked plasmid delivery, because of the greatly increased transformation efficiency, as evidenced by Taniyama, et al. (2001) Circulation, 104: 2344-50. Hence, the Artisan, before, and even after the date of invention, recognized that the type of vector was critical to the invention and demonstration of any single vector would not reasonably predict the use of any other vector.

With regard to the treatment of disease not in the tissue to which the vector is administered, it has been, and remains widely recognized, through the work of the inventors that the system acts in an autocrine or paracrine manner. Such is provided by Nakamura, et al. (1995) Biochem. Biophys. Res. Comm., 215(2): 483-88 (ABSTRACT), and the later published

article of Hayashi, et al. (1996) Biochem. Biophys. Res. Comm., 220: 539-45 (ABSTRACT). Hence, the HGF which is subsequently made has been, and remains, considered to be effective for increasing proliferation of blood vessel endothelial cells local to the site of expression. Hence, the Artisan would necessarily recognize that these methods would not be reasonably predicted to act on tissues that are not the tissue which is expressing the HGF.

With regard to the use of promoters, the Artisan would recognize that the use of non-constitutive promoters would not reasonably predict treatment. The reason for such is simple: without the protein being expressed, and expressed at high enough levels to have the therapeutic effect, the treatment would be ineffective.

The Level of Predictability in the Art

Because of the art, as shown above, does not disclose enough information to reasonably predict that any vector could be used, that any tissue could be treated by injection into any particular muscle, or that any promoter could be used, the Artisan could not predict, in the absence of proof to the contrary, that such applications would efficacious in any therapeutic treatment.

Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

The Level of One of Ordinary Skill in the Art at the Time of Invention

The level of one of ordinary skill in the art at the time of invention was advanced, being that of a person holding a Ph.D. or an M.D.; however, because of the immaturity of the art, and its unpredictability, as shown by the other factors, one of skill in the art at the time of invention

by Applicant would not have been able to make and/or use the invention claimed without undue experimentation.

The Amount of Direction and Guidance Provided By Applicant

Applicant's specification broadly describes treatment of many diseases by HGF (pp. 1-2), a description that HGF has short half-life in the blood (p. 2), and recognition that if HGF could be produced locally, the problems with its short half-life may be overcome. A Broad description of the HGF gene is then provided (p. 8), a description of treating various diseases by gene therapy (pp. 9-10), a description of liposomes and HVJ-liposomes (pp. 11-12), methods for introduction of the gene into the body (p. 12), types of viral vectors (pp. 12-13), methods of administration (p. 13), *in vivo* and *ex vivo* treatments (pp. 13-15), and predicted amounts of vector to administer (p. 15).

However, given the state of the art, such broad guidance does not constitute the specific direction and guidance the artisan would require to reasonably predict that any tissue could be treated, that any other tissue than the tissue which is being injected with vector could be treated, that any vector could be used, or that any promoter could be used.

The Existence of Examples

Applicant's examples demonstrate the making of HVJ-liposomes comprising a plasmid where HGF is under the control of the Sra promoter (COMPARATIVE EXAMPLE 1), similar vectors that express TGF-beta (COMPARATIVE EXAMPLE 2), expression of HGF in rat coronary endothelial cells after HVJ-liposome transformation *in vitro* (TEST EXAMPLE 1), demonstration that HGF causes proliferation of endothelial cells (TEST EXAMPLE 2), HGF expressed from VSMC causes endothelial cells to proliferate (TEST EXAMPLE 3), and also

works for rat endothelial cells (TEST EXAMPLE 4), mixed populations of VSMC expressing HGF and either human (TEST EXAMPLE 5) or rat (TEST EXAMPLE 6) endothelial cells, causes growth of the endothelial cells, a demonstration that HGF does not cause VSMC proliferation (TEST EXAMPLE 7), a demonstration that the HVJ-liposome expressing HGF causes blood vessel growth in rat coronary muscle (EXAMPLE 8), and a demonstration that TGF-beta increases proliferation of cartilage cells in similar vectors (EXMPLE 9).

However, given the lack of reasonable predictability in the art, even in the face of Applicant's disclosure, the Artisan would not reasonably predict that any vector could be used, that any tissue could be treated, that tissues not the muscle which is being administered the vector could be treated, or that any non-constitutive promoter could be used.

The Quantity of Experimentation Needed to Make and/or Use the Invention

Because of the lack of working examples, insufficient guidance and direction provided by Applicant, the inherent unpredictability of the art, and the nature of the invention, even in the face of an advanced level of skill in the art, one of skill in the art would be required to perform a large amount of experimentation to make and/or use the invention within the full scope as claimed by Applicant. Such experimentation would be required to determine the types of vectors that could be used, the tissues that could be treated, and the types of promoters that would produce enough protein for a long enough period of time to effect treatment.

Conclusion

Given the level of experimentation, Applicant's claims are only enabled for that scope provided at the beginning of this rejection.

Claims Free of the Prior Art

The claims are free of the prior art of record.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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